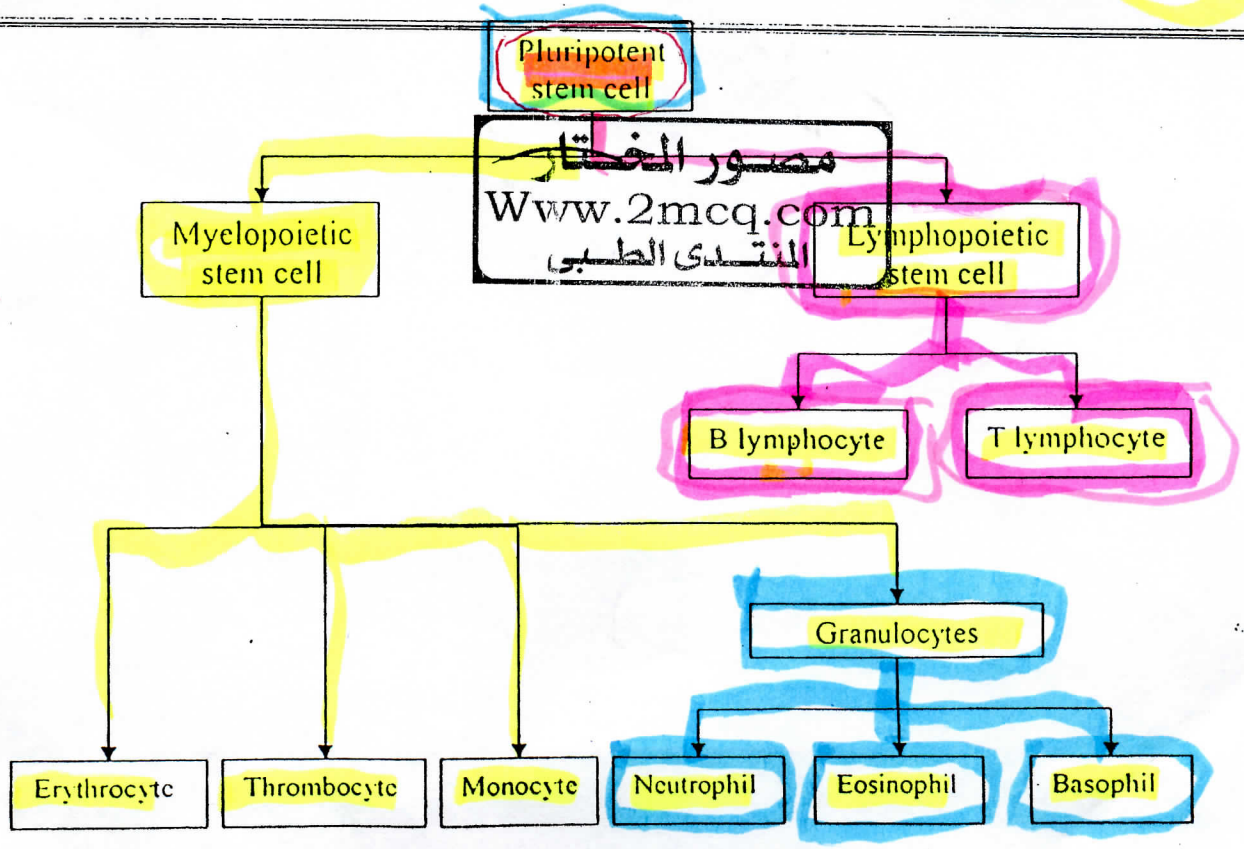
Hematology

The blood is composed of plasma and 3 cell types:

- *Red blood cells* (*erythrocytes*) → Carries O_2 & CO_2.
- *White blood cells* (*leucocytes*) → Protects against infection
- *Platelets* (*thrombocytes*) → Control bleeding

Hemopoiesis

- *Definition:* it is the process of formation of blood cells.
- All blood cells are derived from pluripotent stem cells.
- By birth, hemopoiesis occurs only in red bone marrow.
- In adults red bone marrow is found in flat bones [sternum, pelvis, vertebrae] & in proximal ends of humeri & femora.
- In some diseases hemopoiesis occurs in the liver & spleen (Extramedullary hemopoiesis).



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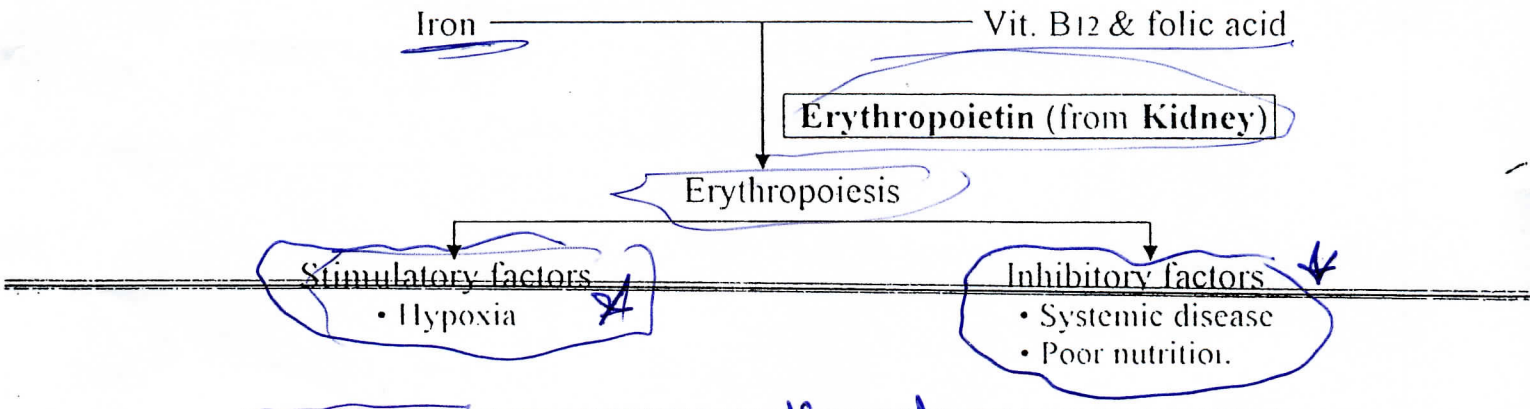
- Notes on Red blood cells

Erythropoiesis: the process of RBC formation.

Erythropoiesis: Pro-erythroblast → erythroblast → Normoblast → **Reticulocytes** → Mature RBCs

Bone marrow — Peripheral blood

- Normal life span of RBC is 120 days.



Reticulocytes

- Reticulocytes are young RBCs newly released from the marrow.
- They are slightly larger and bluer than mature RBC.
- Reticulocytes form 1 % of total peripheral RBCs.
- **Reticulocytosis indicates an active marrow.**
- **Reticulocytosis indicates hemolysis or loss of blood.**

White blood cells include:

- Granulocyte [Neutrophils, Eosinophils, Basophils]
- Monocytes
- Lymphocyte [T-cell, B-cell]

Platelets

- Platelet are derived from Megakaryocytes in the bone marrow.
- Life span of platelets is 10 days.

Main Symptoms in hematology

- ↓ RBC → Anemia
- ↓ WBC → Infections
- ↓ Plt → Bleeding

Investigations In hematology

- Complete blood count [**CBC**]
- Blood film
- Coagulation [PT, PTT]
- Bony marrow aspiration & Biopsy

*Complete Blood count[**CBC**]*

CBC Parameters:

- Hemoglobin
- Hematocrit
- ~~RBC numbers~~
- WBC number
- Platelet number
- Reticulocyte count
- **Red blood cell indices:**
  1. MCV
  2. MCH
  3. MCHC
  4. RDW

Hematocrit value (Hct) = packed cell volume (PCV):

- It is the volume of packed RBCs in 100 ml blood.
- It is not affected in acute bleeding except after about 12 hours until hemodilution occur.
- ♂ = 40 – 54% ♀ = 37 – 47%
- It ↓ with anemia and ↑ with polycythemia

Blood indices

- Blood indices are **average numbers.**

Mean corpuscular Hb = MCH

- It is the amount of Hb per cell
- Normochromia = 27 - 32 pg/Ery
- Hypochromia → M.C.H < 27 pg/Ery
- Hyperchromia → *MCH* ≥32 pg/Ery

Mean corpuscular volume = MCV

- It is the mean volume of one cell.
- Normocytosis = 80- 100 fL.
- ↑ in Macrocytosis (MCV > 100 fL)
- ↓ in Microcytosis (MCV < 80 fL)

Mean corpuscular hemoglobin concentration = MCHC

- It is the Concentration of Hb in the red cell = 31 – 35%
- The MCHC is similar to MCH as it reflect defects in hemoglobin synthesis

Red cell distribution width = RDW

- This one measure the variability of the size of RBC
- Low RDW signifies a normal, homogenous population of cells.
- Increased RDW occurs When there is large variability between cell = anisocytosis

Blood film

It is the examination of blood cells under the microscope

Erythrocyte (RBC) Morphology

- Normal: 7.5-μm diameter.
- ***Anisocytosis***—variation in RBC size.
- ***Poikilocytosis***—abnormal RBC shapes.

Bone marrow examination

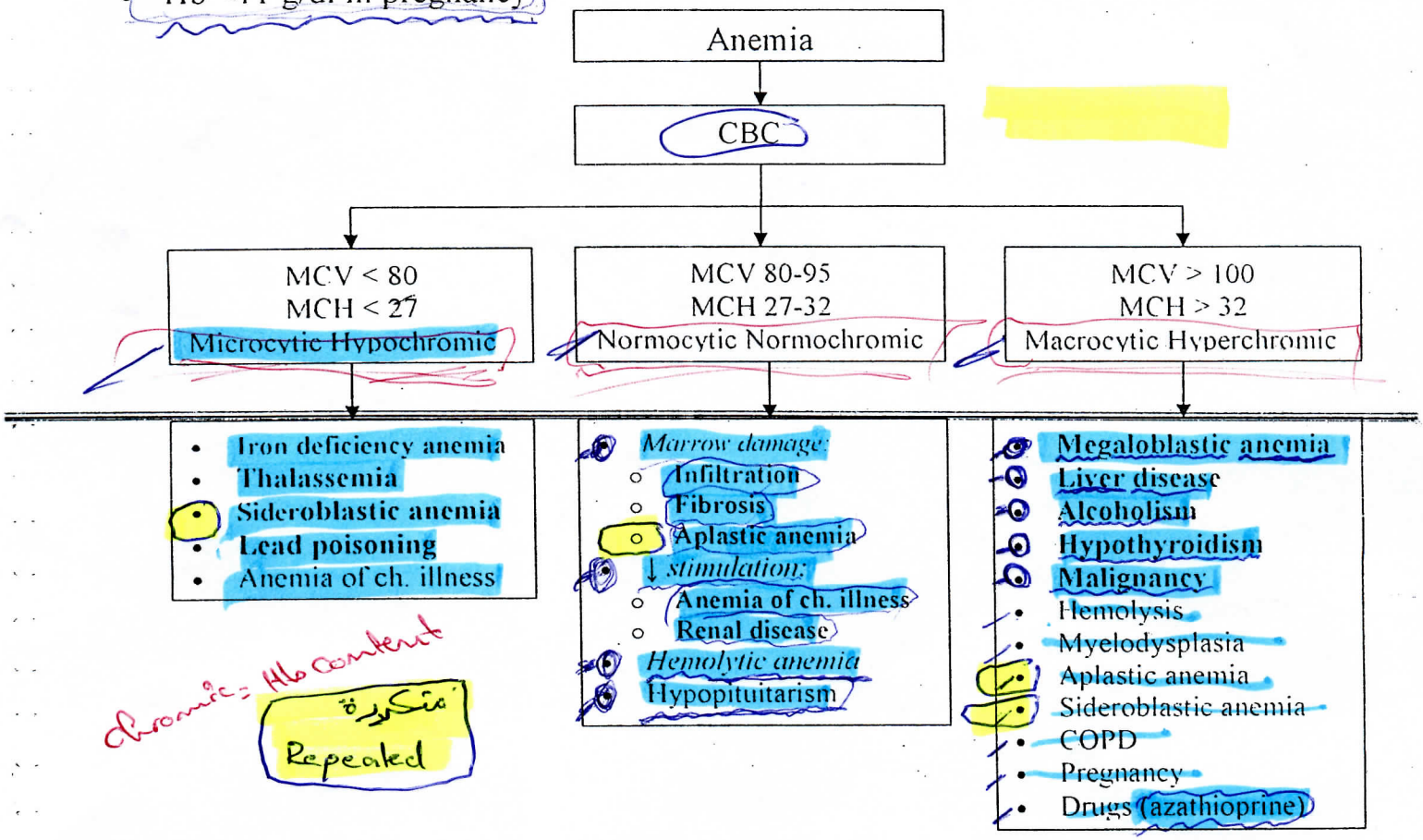
- Bone marrow can be aspirated from the sternum or iliac crest.
- Bone marrow can be biopsied by the use of trephine biopsy from the iliac crest.
- Marrow aspirate is useful for **cytology, cell counts** & assessment of iron stores.

Blood film abnormalities		

Anemia

According to WHO criteria anemia is defined as:

- Hb <13 g/dL in adult male.
- Hb <12 g/dL in adult females.
- Hb <11 g/dl in pregnancy



Chronic = Hb content

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Repeated

Pathophysiology :-

- **Hypochromic microcytic anemia:** the erythropoietic stem cell DNA synthesis is normal, but cytoplasmic synthesis of hemoglobin is impaired.
- **Macrocytic Hyperchromic anemia:** the erythropoietic stem cell cannot produce nucleic acid, and so nuclear maturation is prolonged while Cytoplasmic maturation continues, resulting in abnormally large cells.
- **Normocytic Normochromic anemia:** here the RBCs are normal in morphology but low number is produced.

Iron deficiency anemia

Definition: Anemia due to decreased body iron.

Epidemiology

- Iron deficiency is the most common anemia & most common hematological disease.
- It affects **2 billion** people worldwide.
- Premenopausal women most common cause is excessive menstrual blood loss.
- in men & postmenopausal women the **most common cause is GIT Bleeding**.

Iron metabolism

Iron daily requirement
- ♂ + post menopausal ♀ = 1 mg
- Menstruating ♀ = 1.5 - 2 mg
- Pregnancy = 5-6 mg

- Absorption:
  - Iron is absorbed from the duodenum & upper jejunum.
  - Ferrous iron (Fe^{++}) is more absorbable than ferric iron (Fe^{+++})
  - Absorption is ↑ by acids (*gastric acid ascorbic acid*) & ↓ by *tannates* in tea.
- Iron is transported by **transferrin** & stored as **ferritin** mainly in liver &bone marrow
- In iron ↓ anemia iron stores ↓ → ↓ ferritin.

Etiology

- Chronic blood loss → GIT (Common causes):
  - Hiatus hernia (*Cameron ulcer*)
  - Peptic ulcer (pts on NSAID or Steroid).
  - Hookworms infestation, Schistosomiasis.
  - IBD
  - CA stomach, colon.
  - Other: Diverticulosis, angiodysplasia, telangiectasia.
- → Menstruation
- → Urinary tract
- ↓ intake:
  - Pt not eating meat. [vegetarian pt eat iron but in no-absorbable form].
- Malabsorption:
  - ↓ Gastric acid: → Hypochlorhydria in the elderly,
    → Post-gastrectomy
  - Small intestinal disease e.g. Celiac
- ↑ demand: in children, pregnancy and lactation

Clinical features

Symptoms of anemia [↓ O_2]
- Muscles → Fatigue = Tiredness = Lassitude
- CNS → Headache
- CNS → Lightheadedness & Fainting
- Resp sys → Dyspnea on exertion
- Cardiovascular Sys → Palpitation
- Cardiovascular Sys → In pt with heart disease:
  - Symp of CHF: LLF
  - Angina

Symptoms occurring in iron deficiency:
- **Pica**: the craving to eat unusual substances such as dirt, clay, ice, or hair.
- **Dysphagia** due to **esophageal webs**.
- **Hair loss**, alopecia

Sings
- **Pallor**
  - Skin and mucous membranes pallor [hemoglobin level is 8–10 g/dL]
  - Palmar creases pallor [hemoglobin level is < 8 g/dL]
- Epithelial manifestations:
  - Glossitis (smooth, red tongue), painless stomatitis, and angular cheilitis.
  - **Koilonychia**: spooning of the fingernails. [in Ch. iron deficiency anemia]
- Tachycardia and systolic ejection murmur
- Splenomegaly may occur

Investigations

- **CBC** (Microcytic Hypochromic anemia):
  - ↓ Hb, ↓ Hct, ↓ RBCs count.
  - The MCV < 80 fl (**microcytic**), & MCH < 27 pg (**hypochromic**).
  - ↑ Platelet count suggests bleeding as a cause.
  - Reticulocyte is normal or low, & WBCs count is normal.
  - High RDW (Red Cell Distribution Width) denoting **anisocytosis**
- Blood film (not done regularly)
  - Confirms that the cells are microcytic & hypochromic.
  - Anisocytosis: the RBCs are not of the same size.
  - Poikilocytosis: the RBCs are not of the same shape.
  - Pencil cells & Target cells, may be seen..

- **Iron studies**: Serum iron, transferrin saturation (TIBC), and Transferrin saturation
  1. Serum ferritin is low:
     - Due to reduced or absent body iron stores.
     - Serum ferritin is the best single test to confirm iron deficiency
  2. Serum iron is low.
  3. Total iron capacity (TIBC) (Transferrin level) is high
  4. Transferrin saturation is the ratio of serum iron to TIBC.
     - In Fe-deficiency it is decreased to < 16%. [normally > 30%]

- Lab: ↑ erythrocyte protoporphyrin in peripheral blood.

- Bone marrow examination: (not needed for diagnosis)
  - Erythroid hyperplasia, and Decreased or absent hemosiderin in the marrow
  - Bone marrow examination is not needed for diagnosis.

- **Investigations for the etiology**: As stool analysis to exclude parasitic infestations or occult blood. In some pts Upper & Lower GI endoscopy.

Management

1. Correct underlying disorders
2. **Oral preparation** is the best treatment route.
   - Ferrous sulphate [dose 200 mg of elemental iron daily].
   - Ferrous sulphate tablet contains 65 mg of elemental iron→ given 3 times/ day.
   - *Side effects*
     - Nausea.
     - Abdominal pain.
     - Black stool.
     - Diarrhea or Constipation
   - Treatment is continued for 3 months after the hemoglobin has returned to normal to replenish iron stores.
3. **Parenteral preparations** (IM or IV) are used **only** is in patients who are unable to tolerate oral therapy or pt with malabsorption or continuing severe blood loss.
   - Parenteral route is associated hypersensitivity reactions (anaphylaxis).
   - Parenteral route does not lead to more rapid repair of anemia.
   - Preparations→Iron sorbitol given deep IM by Z-technique [SE: Painful & causes brown skin discoloration at site of injection]
4. **Blood transfusion:**
   - Blood transfusion is not appropriate unless the pt is severely symptomatic with angina or breathlessness, or to prepare the patient for surgery.
   - Pt with Hb < 8g/dl is likely to need blood transfusion.
   - In pt with heart failure give packed RBC.

Monitoring response to iron therapy:

1. Reticulocytosis starts on 3rd day & peaks at 7th after starting treatment.
2. Hemoglobin rises by rate of 1g/dl per week.
3. Normalization of the hemoglobin level (1 month)
4. Repletion of iron stores (2-4 months).

If the pt is not responding look for another cause of anemia.

Differential diagnosis of microcytic hypochromic anemia			
	Serum iron	**Transferrin saturation**	**Serum ferritin**
Iron deficiency anemia	Low	Low	Low
Anemia of ch. illness	Low	Normal	High
Thalassemia	Normal	Normal	Normal
Sideroblastic anemia	High	High	High
Lead poisoning	High	High	High

Anemia of chronic illness

~~**Definition:** It is an anemia that occurs in pts with chronic inflammations (RA,TB,Lymphomas)~~

Pathophysiology: Inflammatory mediators (IL-1, TNF) are responsible:

1. They ↓ production of erythropoietin in kidneys & impair its action in the marrow.
2. Direct inhibition of the bone marrow.
3. They ↑ Hepcidin → inhibits release of iron from the storage sites (e.g. spleen macrophage)
   → inhibit iron absorption from the small intestine.
4. Inflammatory mediators → production of acute phase proteins in which include ferritin

Dx: • **CBC**: Usually *normochromic normocytic* anemia, but can be hypochromic microcytic.
• **Iron studies**: Low serum iron level, normal transferrin level, and high ferritin level.

Rx: Treat underlying cause. Exogenous erythropoietin is effective. Iron is not effective.

Sideroblastic anemias

Definition: they are anemias, caused by disorders in the synthesis of the heme moiety of hemoglobin, and are characterized by trapped iron in the mitochondria of nucleated RBCs named ringed sideroblasts.

Causes

- Hereditary [X-linked, due to an abnormality in pyridoxine (vitamin B_6)]
- Idiopathic
- Secondary (Isoniazid, alcohol-induced, lead poisoning)

Dx:

- **CBC**: Usually hypochromic microcytic anemia, but can normocytic or macrocytic.
- **Iron studies**: High serum iron levels, High transferrin saturation, High ferritin levels
- Bone marrow reveals the **ringed sideroblasts**

Rx: • Stop the offending drug.
• Pyridoxine is effective only in hereditary causes

Megaloblastic Anemia

Definition: A group of anemias caused by deficiency of B_{12} or Folic acid.

	Vit B_{12}	Folic acid
Metabol	• Requirements: 1 micro gm/d. • Sources : Animal sources • Absorption: Ileum • Store: 3-5 mg in liver can supply for 5 yr	• Requirements: 50 micro gm/d • Sources: Animal and Vegetables. • Absorption: duodenum and Jejunum. • Stores: 5-15 mg, can supply for months.
Causes	1. ↓ Intake: rare & occurs in vegetarians. 2. ↓ Intrinsic factor: Pernicious anemia (most common cause) 3. Intestinal disease: ▪ Ileal disease e.g. Crohn's disease ▪ Bacterial overgrowth syndrome ▪ Diphyllobothrium latum.	1. ↓ Intake (common in alcoholics, elderly) 2. Intestinal disease e.g. Celiac disease 3. ↑ demand (pregnancy) 4. Drugs: ▪ Phenytoin ▪ Methotrexate ▪ Azathioprine

need Intrinsic or Extrinsic factor

Note on absorption of Vit B 12:

Parietal cells of stomach secrete an **intrinsic factor** which combines with Vit. B_{12}. reaching the terminal ileum the B_{12} – intrinsic factor complex where it is absorbed → after absorption Vit. B_{12} binds to **transcobolamin II** to be transported to tissues.

Clinical Picture

- Symptoms & signs of anemia
- GIT manifestations:
  - Dyspepsia
  - Red beefy tongue which is painful
  - Splenomegaly
- **Neurological manifestations occur only in Vit B_{12} deficiency:**
  - Posterior column: paresthesia, ↓ vibration & joint position sense.
  - Pyramidal: spastic weakness, hyperactive reflexes, +ve Babinski
  - Subacute combined degeneration = Posterior column + Pyramidal tracts.
  - Cerebral: dementia, psychosis (megaloblastic madness), optic atrophy
  - Peripheral neuropathy
  - Autonomic neuropathy
  - Note: <u>There is no correlation between severity of anemia and neurologic manifestations of B_{12} deficiency.</u>

Note: In pregnancy, even a mild folate deficiency is associated with defects in neural **tube closure in the fetus, so folate supplements should always be given to pregnant.**

Investigations

- **CBC:** (Macrocytic, Hyperchromic)
  - ↓ Hb, Hct, & RBC
  - MCV >100 (macrocytic anemia)
  - ↓ WBC (neutropenia) & ↓ Platelets (thrombocytopenia) may occur
  - Reticulocyte count is low but increases with treatment.
- **Peripheral blood film:**
  - Macro-ovalocytosis.
  - Howell-Jolly bodies and basophilic stippling.
  - **Hypersegmented neutrophils**.
- **Bone Marrow:** hyperplastic bone marrow with **megaloblastic** RBCs.
  [Megaloblasts occur only in Vit B_{12} ↓ + Folate ↓ & Not in other causes of macrocytosis]
- **Lab:**
  - ↑ Serum bilirubin & ↑ LDH due to intramedullary haemolysis
  - **Homocystine levels:** elevated in both deficiency states.

- **Folate deficiency** is diagnosed by measurements of:
  - Serum folate, which shows current level of folate.
  - Red cells folate, indicate folate levels over the preceding 6 weeks. (better)
- **Vit B_{12} deficiency** is diagnosed by:
  - Methylmalonic acid levels (elevated) is the diagnostic procedure of choice.
  - Vit B_{12} serum levels
  - *Schilling test:* it tests for the presence of intrinsic factor and intestinal function to find out the cause of vitamin B_{12} deficiency.
    Procedure: Vit B_{12} is given I.M. to saturate stores then give B_{12} orally labeled with radioactive material, normal person secrete 25% of radioactive B_{12} in urine but Pt with pernicious anemia, will secrete < 5%, this indicates poor absorption through the small intestine. We can repeat the test after intake of intrinsic factor.

DDx of Macrocytositic anemia

1. Megaloblastic causes [Vitamin B_{12} deficiency, Folate deficiency]
2. Alcohol
3. Chronic liver disease
4. Hypothyroidism
5. Myelodysplasia

Treatment

Note: If a pts with megaloblastic anemia due to Vit B_{12} deficiency is treated with folic acid, the anemia will be corrected but the neurologic abnormalities will progress.

- Vit B_{12} deficiency: **IM Hydroxycobolamine** 1000 µg IM in five doses 3 days apart followed by maintenance therapy of 1000 µg every 3 months for life.
  - Note: Treatment may → ↓ potassium levels & rapid depletion of iron stores.
- Folate deficiency: **Oral folic acid** 5 mg daily for 3 wks to treat acute deficiency followed by maintenance therapy of 5 mg once weekly.

Pernicious anemia

It is the commonest cause of Vit B_{12} (cobalamin) deficiency.

Definition: Pernicious anemia is a condition in which the portion of gastric mucosa that contains the parietal cells is destroyed through an autoimmune mechanism. The parietal cells secrete intrinsic factor, which is essential for cobalamin absorption.

Epidemiology

- Age: usually after age 40.
- Gender: more in females.
- More in persons of blood group A.

Clinical presentation

- Anemia, GIT, and Neurologic symptoms (see above)
- Other features include:
  - May be associated with other autoimmune diseases e.g., thyroid diseases, vitiligo, hypoparathyroidism, and Addison's disease.
  - It is associated with premature graying of hair or blue eyes.
  - ↑ Risk of gastric cancer.

Investigations

- Anti-parietal cell antibodies are positive in > 90% but are found in normal people.
- Anti-intrinsic factor antibodies are positive in 60% and are diagnostic.

Treatment: As Vit.B12 defieincy

Hemolytic anemia

Overview

- Hemolysis = RBC life < 120 days.
- BM can ↑ production of RBC by 8 times, but when it fails to compensate → anemia

Physiology of red cell destruction

- Extravascular hemolysis
  - In Extravascular hemolysis the RBC are removed by macrophages of the reticuloendothelial system mainly in spleen → **Splenomegaly**.
  - Breakdown of Hb → ↑ unconjugated bilirubin → **Jaundice**.
  - The ↑ bilirubin will be excreted by liver → ↑ risk of **pigment stones**.
    → ↑ urine Urobilinogen [not bilirubin]
- Intravascular hemolysis
  - Intravascular destruction indicates fragmentation of RBC within in the circulation.
  - Hb released bind to proteins called **Haptoglobins**, and they from a complex removed by the liver, so in hemolytic anemia Haptoglobin level is **Decreased.**
  - When the binding capacity of haptoglobin is exceeded, free hemoglobin is filtered in the kidney and converted to hemosiderin in renal tubular cell → **Hemosiderinuria** After that **Hemoglobinuria** (hemoglobin in the urine) → Black urine.

Clinical picture → Anemia, Jaundice, Splenomegaly

Causes of hemolytic anemias	
Congenital	Acquired
Membrane defects 1. Spherocytosis 2. Elliptocytosis Hemoglobinopathies 1. Sickle cell disease 2. Thalassemia Red cell enzyme defects 1. G6PD deficiency 2. Pyruvate kinase deficiency	• Autoimmune 1. Infections: EBV, Mycoplasma 2. Systemic lupus erythematosus SLE 3. Chronic lymphocytic leukemia CLL • Non-immune 1. Microangiopathic hemolytic anemia 2. Prosthetic heart valve 3. Drug- or toxin-induced 4. Paroxysmal nocturnal hemoglobinuria

Investigation		
	Hemoglobin	↓
	MCV, MCH	Normocytic or Macrocytic
	Reticulocytes	↑ **Reticulocytosis**
	Bilirubin	↑
	LDH	↑
	Haptoglobin	Reduced to absent
	Blood film	**Polychromasia [↑ reticulocytosis]**
	Urine	↑Urobilinogen

Spherocytosis

Hereditary spherocytosis is the **most common inherited hemolytic anemia.**

Etiology

- Inheritance is **Autosomal dominant.**
- There is abnormality RBC membrane protein **spectrin** or **ankyrin** that causes the RBC to become spherical in shape with ↑ rigidity.

Clinical features

- Anemia (Weakness, Dyspnea, Palpitations, Pallor) + Jaundice +Splenomegaly
- Pigmentary gallstones are present in 50% of pt & may cause cholecystitis.
- Ankle ulcers.
- Aplastic crises associated with parvovirus B19 infection may occur.

Investigations

- As all hemolytic anemias (*Anemia, Reticulocytosis, Indirect hyperbilirubinemia*)
- CBC: **Microcytosis with Hyperchromia** (↑MCH)
- Blood film → **Spherocytes.**
- Osmotic fragility test is +ve: When RBC are added to hypotonic solution the RBC are abnormally fragile.

Management

- Splenectomy improve the decrease in lifespan but spherocytosis persists.
- Folic acid prophylaxis for life.
- If cholecystectomy required, perform splenectomy also to ↓ risk of recurrent gallstones.

Management of pt for splenectomy:

- Splenectomy should be delayed until the child is > 6 ys to ↓ the risk of invasive infection caused by encapsulated bacteria.
- Vaccination : Pneumococcal, Haemophilus influenzae, Meningococcal & influenza vaccines 2-3 weeks before splenectomy.
- Pneumococcal repeated every 5-yrs & influenza annually.
- Life-long prophylactic penicillin [If penicillin-allergic → erythromycin]

Glycolytic enzymatic defects

➢ Glucose-6-phosphate dehydrogenase deficiency (G6PD)

It is the **most common RBC enzymatic defect.** It may occur as an **acute** hemolytic disease induced by infection or medications, or as a **chronic** hemolytic disease.

Epidemiology

- X-linked recessive
- Mediterranean, Arabic, Asian, and African.

Pathophysiology:

G6PD enzyme synthesizes NADPH which protects the RBC from oxidative stress via glutathione. So G6PD Deficiency → RBC damage on exposure to oxidants.

Triggers of hemolysis

1. Infection
2. Fava beans
3. Drugs:
   - Antibiotics: sulphonamides, nitrofurantoin, ciprofloxacin, dapsone
   - Salicylates
   - Antimalarials

Clinical features

- Symptoms occur 24—48 hours after exposure to oxidant.
- Hemolysis occurs, resulting in abdominal pain, V/D, fever, and jaundice.
- Hepatosplenomegaly may be present.

Laboratory findings

- Hemoglobinuria
- Blood film: **Bite cells** (RBCs with bite of membrane missing) & Heinz bodies.
- *Diagnosis:* Low levels of G6PD in RBCs

Treatment: Transfusions as needed; splenectomy not beneficial.

➢ **Pyruvate kinase (PK) deficiency:** it is **autosomal recessive** ↓ PK enzyme → ATP depletion and decreased RBC survival. **Diagnosis**: ↓ PK activity in the RBCs. **Management** includes transfusions & splenectomy for severe disease.

Thalassemia

Definition: Thalassemia is an **autosomal recessive** syndromes of anemias characterized by defective synthesis of one of the Hgb chains.

Pathophysiology

- Normally the major Hgb in RBCs is hemoglobin A_1 [2 α + 2 β]. Other hemoglobins present in small amounts are Hgb A_2 [2 α + 2 δ] & Hgb F [2 α + 2 γ].
- **α-Thalassemia** results from **defective α-globin chain synthesis** and **β-thalassemia** results from **defective β-globin chain synthesis.**
- Both types of thalassemia → hemolysis → ↑bone marrow activity → bone marrow hyperplasia → ↑ in the size of bones in the face and skull.

α-Thalassemia: more in Asian.

There are 4 α-globin genes per cell. So there are 4 disease states:

1. **Silent carrier:** 1 α-globin gene is deleted. Pts have **no anemia.**
2. **α-Thalassemia minor:** 2 α-globin genes are deleted. Pts **mildly anemic.**
3. **Hgb H disease:** 3 α-globin are deleted. Anemia is lifelong and severe.
4. **Fetal Hydrops:** 4 α-globin genes are deleted. Causes fetal death.

β-Thalassemia: more in Mediterranean.

There are only two β-globin genes per cell, so there are only two disease states:

- **β-Thalassemia major** (**Cooley's anemia** or homozygous β-thalassemia)
  - Both genes for β-globin are abnormal.
  - *Clinical features*:
    - Disease begins in infancy around 6 months of age.
    - Anemia + jaundice + Hepatosplenomegaly.
    - If untreated, bone marrow hyperplasia → **Thalassemia facies = Mongloid facies** (frontal bossing, prominent cheekbones due to maxillary hyperplasia).
    - Ankle ulcers may occur.
  - *Investigations*:
    - As all hemolytic anemias (Anemia, Reticulocytosis, Indirect hyperbilirubinemia)
    - CBC: severe **hypochromia** and **microcytosis**.
    - Blood film: show **Target cells**.
    - **Electrophoresis**: Low or absent Hb A_1 and elevated Hb F & Hb A_2.
    - Skull X-ray shows "hair on end" appearance.
  - *Management* → Treatment includes **lifelong transfusions** and often splenectomy.
  - *Complications* → **Hemochromatosis** is caused by iron in transfused RBCs. Chelation of iron with deferoxamine increases iron excretion & delay hemochromatosis.
- **β-Thalassemia minor** (heterozygous β-thalassemia or β-thalassemia trait) causes a **mild asymptomatic anemia** with Hgb levels 2-3 g/dL below age-appropriate norms. Investigations shows hypochromia and microcytosis with target cells. No treatment is required.

Sickle cell disease

Epidemiology

- More in black
- **Autosomal recessive**

Etiology and pathophysiology

- SS disease is caused by a single amino acid substitution of valine for glutamic acid on the number 6 position of the β-globin chain of Hb.
- The mutation results in polymerization of Hb when the RBC is exposed to low oxygen or acidosis. [HbF strongly resists polymerization].
- Polymerization of Hgb → Sickle shaped RBC → ↓RBC lifespan **[Hemolysis]**
  → Occlusion of small vessels → ischemia & infarction
- **SS disease → two genes for Hgb** S (homozygous).
- **SS trait → one gene for Hgb** S (heterozygous): they have no anemia and the red cell morphology is normal but resistant to *falciparum* malaria.

Clinical presentations

→ **Crisis**
→ Chronic hemolytic anemias

Sickle-cell crises

- **Vaso-occlusive crisis** (most common crisis) Extremely painful crisis due to bone infarction. In children hands & feet affected (**dactylitis**). Other bones are affected.
- ***Acute chest syndrome (Sickle chest syndrome)***: the most common cause of death in adult with sickle disease. Bone marrow infarction (thrombotic crisis) → fat emboli to the lungs → sickling and infarction of the lung. Fatal if not treated.
- ***Sequestration crisis:*** Thrombosis of venous outflow → acute painful enlargement.
  In children the spleen is the most common site → splenomegaly.
  In adults the liver is most common site.
- Aplastic crises
  - caused by infection with parvovirus, or folic acid deficiency
  - Sudden fall in hemoglobin + low reticulocyte count.

Sickling crisis may be precipitated by:	Sickling crisis is treated by
1. Hypoxia 2. Dehydration 3. Infection 4. Stress	1. Oxygen 2. Intravenous fluids 3. Opiate analgesics 4. Antibiotics

Other features sickle cell disease:

- Splenic infarcts → **Hyposplenism** (autosplenectomy) → ↑ pneumococcal infection
- **Salmonella osteomyelitis** occurs in areas of infracted bone.
- Pigmented gall stones are common.
- Retinopathy, acute renal papillary necrosis, leg ulcers may occur.
- **Priapism**: painful sustained erection.
- Pregnancy is dangerous.

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2009

Investigations

- As all hemolytic anemias (*Anemia, Reticulocytosis, Indirect hyperbilirubinemia*)
- CBC: Normocytic normochromic anemia.
  - leukocytosis is common.
- Blood film → **Sickle cells.** + Features of hyposplenism.
- **Hemoglobin electrophoresis** shows 80–99% HbS with no normal HbA. HbF may be elevated to about 15%. This test confirms the diagnosis. The Hb A2 is not increased. [unlike β-thalassemia in which HbA2 is ↑]

Treatment

- **Hydroxyurea (hydroxycarbamide)** a chemotherapeutic agent that ↑ HbF.
- **Daily oral penicillin prophylaxis** is started in the first months of life to decrease the risk of *S. pneumoniae* infection.
- **Daily folic acid** is given to prevent folic acid deficiency.
- **Vaccination:** against Pneumococcal, Haemophilus influenza, & Hepatitis B.

Prognosis

- ~~Median life expectancy is in the forties.~~
- **Long-term complications** include delayed growth and puberty, cardiomegaly, hemochromatosis, cor pulmonale, gallstones, poor wound healing, avascular necrosis of the femoral and humeral heads, and diminished cognition.

Autoimmune hemolytic anemia [AIHA]

Definition: they are anemia resulting from ↑ RBC destruction due to RBC autoantibodies.

Autoimmune hemolytic anemia are divided in to **Warm** or **Cold** according to at what temperature the antibodies best cause Hemolysis.

Epidemiology: more in middle aged females.

Etiology

- Idiopathic [Most common cause]
- Autoimmune disease: SLE, RA, IBD.
- Neoplasia: e.g. Lymphoma, CLL
- Drugs: e.g. methyldopa
- Infections: e.g. Mycoplasma, EBV [causes Cold type]

Clinical picture

- Anemia + Jaundice
- Cold type: Raynaud's phenomena on exposure to cold.

Investigations

- CBC: normocytic, normochromic anemia, or macrocytic hyperchromic
- Blood film: polychromasia, spherocytosis, fragmentation (schistocytes).
- **Direct antiglobulin test (Coombs' test)**
  - In both Cold and Warm AIHA is positive, and it is the definitive diagnostic test.
  - In this test the addition of anti-human immunoglobulin antibodies will show the autoantibodies on RBC surface by causing agglutination.

Treatment

- Treat the underlying cause
- **Corticosteroids** [80% of pt responds, and response may take 3 weeks to occur]
- **Splenectomy** [if steroids didn't work]

Comparison		
	Warm (80% of pts)	Cold (20% of pts)
Antibody	IgG	IgM
Active temperature	37°C	4°C
Response to therapy		
Steroids	Good	Poor
Splenectomy	Good	Poor
Glove, warmth	None	Good

Aplastic anemia

Definition: A **pancytopenia** associated with a hypoplastic bone marrow.

Etiology and pathogenesis

- **Congenital** e.g. autosomal recessive (Fanconi's anemia)
- **Acquired**:
  - Idiopathic (most common cause)
  - Radiation
  - Drug induced (gold, chloramphenicol, NSAIDs, carbamazepine, phenytoin)
  - Viral infection (Parvovirus, Hepatitis viruses A, B and C, CMV and EBV)
  - Chronic benzene exposure

Clinical features

- May occur at any age. in either sex.
- Onset rapid (over a few days) or slow (over weeks or months).
- Symptoms and signs are caused by bone marrow failure (↓RBC, ↓WBC, ↓ Plt).
- Liver, spleen and lymph nodes are not enlarged.

Investigations

- Anemia is normocytic or mildly macrocytic with a low or absent reticulocyte.
- Leucopenia and Thrombocytopenia are usual.
- Bone marrow is hypoplastic with increased fat (fat/hemopoiesis ratio >75:25%)
- Remaining hemopoietic cells are normal appearance and there is no evidence of malignancy. Megakaryocytes are particularly reduced.

Treatment

Supportive: blood transfusion & prevention and treatment of infection
Immunosuppressive: Antilymphocyte globulin (ALG) + Ciclosporin
Stem cell transplantation [Allogeneic transplants is successful in 80% of pts]

Prognosis: Poor

Complications of blood transfusion

1. Infections [HIV, and hepatitis B and C infection, malaria]
2. Minor febrile reactions [common, less likely if red cells are leucodepleted]
3. Hemolytic reactions
4. Severe allergic reactions [in pts with IgA deficiency]
5. Transfusion-related lung injury [due to aggregation on neutrophils in lung capillaries]
6. Problems caused by massive transfusions [hypocalcemia, bleeding]
7. Chronic iron overload → 2ndry hemochromatosis (cardiac, liver & endocrine damage)
8. variant Creutzfeldt-Jakob disease (vCJD)
9. Immune suppression [worsen prognosis of CA colon, and ↓ risk of rejection for renal transplant pt (good thing)]
10. Graft-versus-Host disease [Rare: lymphocytes from donor survive and attack the host]

Acute, severe hemolytic reactions

Severe acute hemolytic reactions are rare, and caused by only by ABO incompatibility. The patient may develop pyrexia and chest or abdominal pain and pass black urine, rapidly progressing to shock, acute renal failure and DIC.

If a hemolytic reaction is suspected, you should:

- stop the transfusion immediately
- give intravenous hydrocortisone and chlorphenamine
- check the patient's identity and details of the donor blood
- return the blood to the transfusion laboratory with a fresh sample of the patient's blood
- call for senior help and resuscitate as needed.

Myeloproliferative disorders

The myeloproliferative disorders are a group of four diseases caused by clonal proliferation = neoplasia of hematopoietic stem cell:

1. Myeloid leukemias.
2. Myelofibrosis.
3. Polycythemia rubra vera.
4. Essential thrombocytosis.

Myelofibrosis

Definition: Myelofibrosis is a disease in which bone marrow becomes fibrotic.

Etiology: It may be a result of other myeloproliferative diseases or may present as a primary disorder.

Pathophysiology: There is hyperplasia of abnormal megakaryoctyes, which releases platelet derived growth factor (PDGF) which stimulates fibroblasts → fibrosis. Extramedullary hematopoiesis (in spleen and liver) occurs as a result

Clinical presentation

Typically the pt is around 50 yrs with anemia & splenomegaly (often massive and causing pain), and systemic symptoms e.g. weight loss and fever.

Investigations

- **CBC**: anemia. ↑ WBC & Plt early in the disease. [pancytopenia late]
- **Blood film**: immature white and red blood cells (**leukoerythroblastic** changes) with red cells are shaped like **teardrops** and **giant platelets** may be seen.
- **Bone marrow aspiration**→ Dry tap.
- **Bone marrow biopsy** → hypercellular bone marrow with extensive fibrosis.
- High urate and LDH (reflect increased cell turnover)
- Folic acid deficiency is common

Treatment

- Supportive Rx, sometime with Splenectomy to improve blood cells count.
- Folic acid supplement
- Cytotoxic drug hydroxycarbamide may control spleen size.
- BM transplant in young pts.

Prognosis

- Median survival is 4 years from diagnosis.
- The disease may progress to acute leukemia.

Polycythemia

Definition

- **Polycythemia** (erythrocytosis): it is an increase in hemoglobin concentration above normal. It may be true or spurious.
- **True polycythemia** exists when the total red cell mass (RCM) is increased above normal.
- **Spurious (pseudo or stress)** polycythemia exists when an elevated hemoglobin concentration is caused by a reduction in plasma volume.

Etiology

- **True polycythemia**
  - *Primary* → Polycythemia rubra vera (PRV)
  - *Secondary*
    - Erythropoietin appropriately increased
      - High altitude
      - Cyanotic congenital heart disease
      - Chronic lung disease (COPD, Obstructive sleep apnea)
    - Erythropoietin inappropriately increased
      - Renal disease: Renal cell CA, renal cyst, hydronephrosis
      - Tumors: Uterine fibroid, hepatocellular CA, cerebellar hemoangioma
- **Relative (spurious) polycythemia**
  - Plasma volume depletion [e.g. Diuretic therapy, Dehydration]
  - Stress (pseudo-polycythemia) (Gaisbock syndrome)

Polycythemia rubra vera (PRV)

Definition: PRV is a myeloproliferative disorder caused by clonal proliferation of a marrow stem cell leading to an ↑ in red cell volume ± ↑ granulocytes & platelets.

Epidemiology

Age: > 40 years
Gender: male = females
Genetics: mutation in JAK2 is present in approximately 95%

Clinical features

- **Plethoric appearance** and conjunctival suffusion.
- **Pruritis**, typically after a hot bath.
- Hyperviscosity may lead to headaches and visual disturbance.
  Abnormal Plt function → Thrombosis [DVT, Stroke]
  Abnormal Plt function → Hemorrhage
- Enlarged spleen is found in 75% of pts [not found in other causes of polycythemia]
- Hypertension in a 1/3 of pts
- Peptic ulcer are common

Investigations

- CBC: → ↑ Hct, ↑Hb, ↑ RBC and ↑ Red Cell Mass [RCM].
  → 75% of pts have ↑WBC & ↑ Plt.
- Neutrophil alkaline phosphatase (NAP) is raised, and ESR is low.
- The erythropoietin level is low.

Criteria for the diagnosis of PRV	
A1 Raised red cell mass (>25% above predicted) A2 Absence of secondary polycythemia A3 Palpable splenomegaly A4 Presence of an acquired genetic abnormality	B1 Thrombocytosis (platelet count >400 x 10^9/l) B2 Neutrophil Leukocytosis (>10 x 10^9/l) B3 Splenomegaly on ultrasound B4 Spontaneous growth of red cell precursors in vitro without added erythropoietin
A1+A2+A3 or A4 establish Dx of PRV. A1+A2 + two of B establish Dx of PRV	

Treatment

- Aspirin to ↓ risk of Thrombosis.
- Regular venesection is used ↓ hyperviscosity.
- Chemotherapy (e.g. oral hydroxyurea or interferon) to inhibit bone marrow.

Prognosis

Median survival is about 16 years. Up to 30% of pts develop myelofibrosis. Acute myeloid leukaemia occurs in up to 5% of pts.

Essential thrombocytosis

Overview:

- It is a malignant proliferation of Megakaryocytes → persistent elevation of the blood platelet count (thrombocytosis) usually with Plat. Count > 1 million/ml
- Pt around 60 years and may present with thrombosis or hemorrhage, depending on whether the platelets are functioning or not.
- Rx: • Asymptomatic pts with count < 1 million → observation + aspirin
  • Symptomatic pt or count > 1 million → hydroxyurea + aspirin.

Differential diagnosis of thrombocytosis	
Primary	Reactive [Plt count < 1 million]
1. Essential thrombosis 2. As part of other myeloproliferative disorder, e g. PRV, CML myelofibrosis	1. Iron deficiency 2. Hemorrhage or hemolysis 3. Trauma, postoperatively 4. Infection, inflammation (RA) 5. Malignancy 6. Hyposplenism or postsplenectomy

Hematological malignancies

Hematological malignancies arise from a single cell in the bone marrow, thymus or peripheral lymphoid system. This cell undergoes a mutation leading to malignant transformation. Transformed cells either proliferate excessively or are resistant to apoptosis.

Definitions

• *Leukemia*: are malignant disorders of the hematopoietic stem cell compartment, characteristically associated with increased numbers of white cells in the bone marrow and/or peripheral blood. Leukemia is classified by the dominant cell type, and by duration from onset to death. This occurs in *acute leukemia* within a few months in most cases, and is associated with acute symptoms including severe anemia, hemorrhages. The duration of *chronic leukemia* exceeds one year, with a gradual onset of symptoms of anemia.

• *Lymphoma:* Lymphoma is a neoplastic proliferation of lymphoid cells originating in lymph nodes or other lymphoid tissue.

Classification of hematological malignancies		
	Acute	Chronic
Lymphoid	Acute lymphoblastic leukemia (ALL)	Chronic lymphocytic leukemia (CLL) Non-Hodgkin lymphoma Hodgkin lymphoma Multiple myeloma
Myeloid	Acute myeloid leukemia (AML)	Chronic myeloid leukemia (CML) Myelodysplasia (MDS) Myeloproliferative disorders

Causes of neoplasia

1. Genetic predisposition. Certain inherited conditions (e.g. Down's syndrome) and conditions associated with defective DNA repair (e.g. Fanconi's anaemia) or immune suppression (e.g. ataxia telangiectasia).

2. Infections.

Viruses • Epstein-Barr virus: Hodgkin's lymphoma, Burkitt's lymphoma
• Human T-cell leukemia virus (HTLV-1): Adult T-cell leukemia/lymphoma
• HIV-1: High-grade B-cell lymphoma

Bacteria • Helicobacter pylori: gastric lymphoma (MALToma)

Protozoa • Malaria: Burkitt's lymphoma

3. Ionizing radiation causes DNA mutation → ↑ the risk of hematological neoplasia.

4. Toxins/chemicals, e.g. benzene predispose to leukemia and myelodysplasia (MDS).

5. Drugs. Alkylating agents (e.g. melphalan, mustine) predispose to AML, and MDS

Leukemia

	ALL	AML	CML	CLL
Def.	Failure of cell proliferation [blast cells increase]		Failure of cell death (apoptosis) [mature cells increase]	
	Lymphoblasts	Myeloblasts	Neutrophils	Lymphocytes
Epid.	More in males Peak: 1-5yrs[commonest leukemia in children]	More in males > 50 yrs [adult]	More in males 35-55 yrs	More in males > 60 yrs [commonest leukemia in adults]
C/P	Short History < 3 months BM failure → Anemia, Bleeding, Infections Constitutional symptom [fever, anorexia, malaise] **Features due to Tissue infiltration:** o Bones and joint pain. o Hepatosplenomegaly in both. o Lymphadenopathy occurs in **ALL**. o Infiltration of **Meninges, Testes** in **ALL** o Infiltration of **gums** → hypertrophy in **AML** Note: **DIC** occurs in **AML** M3		• May be asymptomatic • Constitutional symptom • Symptom of anemia • **Sternal tenderness** • **Massive splenomegaly** [pain in Lt hypochondrial, early satiety] • Hepatomegaly in 50% of pts • Lymphadenopathy **[unusual]** • Priapism, visual disturbance & headaches due to hyperviscosity	• Most pt asymptomatic • Night sweats & fevers are uncommon and should prompt evaluation for infection. • Symptom of anemia • **Marked Lymphadenopathy** • Moderate splenomegaly • Hepatomegaly uncommon • Association with autoimmune hemolytic anemia.
Ix:	**Lab:** Serum uric acid & LDH may be raised **CBC** • ↓ Hb, ↓ Plt, MCV may be high • Leukocytosis usually but may be normal or low Blood film • May show blast cells • **Auer rods** pathognomonic for AML. **BM exam:** > 20% are blasts [normally < 5%]		**Philadelphia chromosome +ve** **Lab:** ↑Uric acid & LDH **CBC:** • ↓ Hb, ↑ Plt • WBC is always ↑often > 50×10^9/L [mainly neutrophils] • Basophilia • ↑ B_{12} **Leukocyte alkaline phosphatase low** **BM exam:** < 10% are blasts	**CBC** • ↓ Hb, ↓ Plt, • **lymphocytosis > 5×10^9/L** **Immunochemistry:** • B-cells [CD19, CD23 +ve] • T-cell [CD 5 +ve] Low immunoglobulins **BM exam:** < 10% are blasts
Rx	Induction of Remission Consolidation Maintenance	Induction of Remission Consolidation	**Imitinab**	**Chlorambucil ± Fludarabine**

Acute leukemias

Definition: Acute leukemia is a malignant disorder in which hemopoietic blast cells constitute >20% of bone marrow cells. The primitive cells usually also accumulate in the blood, infiltrate other tissues and cause bone marrow failure.

French-American-British (FAB) classification of acute leukemia	
Myeloid	Lymphoid
M0—Undifferentiated by morphology + cytochemistry M1— Little differentiation > 90% blasts M2— Differentiated. 30-90% blasts	**According to cell morphology** **L1** Small cells, high nuclear/cytoplasmic ratio **L2** Larger cells, low nuclear/cytoplasmic ratio **L3** Vacuolated, basophilic blast cells
M3— **Promyelocytic**: highly granular (Auer rods) M4— Myelomonocytic M5—Monocytic differentiation M6— Erythroid differentiation M7— Megakaryoblastic	**According to immunophenotype** **T-cell** phenotype 25% **B-cell** phenotype 5% **Pre-B-cell** phenotype 70%
All subtypes have >20 % blast cells in the bone marrow.	

~~*For Epidemiology, Clinical picture, & Investigations see Table*~~

Treatment

Aim of treatment is to destroy leukemic cells without damaging normal stem cell, and there are 3 phases of treatment:

- *Remission induction:* aims to destroy most of malignant cell by combination chemotherapy.
  - AML: Daunorubicin + Cytarabine + Etoposide
  - ALL: Vincristine + Prednisolone + L-asparaginase + daunorubicin + **Intrathecal methotrexate**.
- *Remission consolidation*: If remission is achieved by induction therapy, residual malignant cells are attacked by consolidation therapy. It includes a number of cycles of intensive chemotherapy with each course requires 4-6 wks in hospital. [stem cell transplantation may be used in pts < 55 yrs].
- *Remission maintenance*: less intensive chemotherapy of repeating cycles for 2-3 years is used to maintain remission in ALL [not AML] and is given at home.

There are some important differences between the treatment of ALL and AML:

- In **ALL: CNS is usually involved and** systemic chemotherapy cannot cross Blood-Brain-Barrier therefore prophylactic Cranial irradiation + High-dose **intrathecal methotrexate** is given.
- In **AML M3: All trans retinoic acid** (ATRA) is given to induce differentiation.

- Supportive Treatment
  - → Blood transfusion to keep Hb > 10 g/dl
  - → Plt transfusion to Keep Plt > 100.000
  - → Treatment of infection
  - → Allopurinol & IV fluids to prevent ↑uric acid →RF

Prognosis

- Without therapy the median survival of pts with acute leukemia is about 5 wks.
- 80% of pts < 60 yrs with ALL or AML achieve remission.
- In AML Promyelocytic [M3] has a good prognosis

Prognostic factors for ALL		
Prognostic factor	Favorable	Unfavorable
Age	2-10 years	< 2- > 10 years
Sex	Female	Male
Race	White	Black
WBC count	< 50.000	> 50.000
Organ involvement	None	CNS involvement
Chromosomal defect	None	Philadelphia translocation t(9;22)
Immunophenotype	FAB L1 type pre-B phenotype	FAB L3 type T or B cell surface markers

Cytotoxic agents		
Cytotoxic	**Mechanism of action**	**Adverse effects**
Vincristine	Inhibits formation of microtubules	Peripheral neuropathy (reversible)
Cisplatin	Causes cross-linking in DNA	Ototoxicity Peripheral neuropathy Hypomagnesaemia
Bleomycin	Degrades preformed DNA	Lung fibrosis
Doxorubicin	Stabilizes DNA-topoisomerase II -→ inhibits DNA & RNA synthesis	Cardiomyopathy
Methotrexate	Inhibits purine and thymidylate synthesis	Myelosuppression Mucositis
Cyclophosphamide	Alkylating agent - causes cross-linking in DNA	Hemorrhagic cystitis, Myelosuppression, Transitional cell carcinoma

Chronic myeloid leukemia

Definition

This is a clonal myeloproliferative disorder characterized by an increase in neutrophils and their precursors in the peripheral blood.

- **Philadelphia chromosome:**
  - The Philadelphia chromosome is present in more than **95%** of pts with CML.
  - **Philadelphia chromosome** results due to a translocation between the long arm of chromosome 9 and 22 – t(9:22).
  - This results in that the ABL gene from chromosome 9 being fuses with the BCR gene from chromosome 22 → BCR-ABL fusion gene which codes for a protein → increased tyrosine kinase activity [which inhibits cell death].
  - The Philadelphia chromosome may occur in ALL.

For Epidemiology, Clinical picture, & Investigations see Table

Natural History

The disease has 3 phases:

- **Chronic phase:** pts is responsive to treatment & disease is controlled.[Platelet count is high] It lasts 3-5 yrs.
- **Accelerated phase:** (not in all pts) disease becomes difficult to control. [there is marked by anemia & Platelet counts falls]
- **Blast crisis:** disease transforms to acute leukemia with [AML in 70% of pts and ALL in 30% of pts] This leukemia resists treatment & Survival is often < 4 months.

Treatment

Chronic phase

- **Imitinab:** is the first line treatment, it is an inhibitor of the tyrosine kinase associated with the BCR-ABL defect, it results in complete hematologic remission of >90% and cytogenetic remission in 76%. If a matched donor is available, it is best to transplant patients in complete remission.
- Hydroxyurea & α-interferon (IFN) will control the raised white cell count.
- Busulfan, it use has been replaced by IFN-α and/or hydroxyurea,
- Splenectomy is not effective
- **Supportive therapy:** See above.

Accelerated phase: Imitinab + Hydroxyurea
Blast crisis phase: As for acute leukemia.

Prognosis

- Median survival is about 4 years.
- Philadelphia chromosome –ve pts have poor prognosis [median survival of < 1 yr]

Chronic lymphocytic leukemia

Definition: Chronic lymphocytic leukemia (CLL) is a B-cell clonal lymphoproliferative disease in which lymphocytes accumulates in the blood, bone marrow and often in the lymph nodes and spleen (lymphocyte count > 5.0×10^9/L)

For Epidemiology, Clinical picture, & Investigations see Table

Clinical Staging for CLL
Stage A: No anaemia or thrombocytopenia + < 3 areas of lymphoid enlargement
Stage B: No anaemia or thrombocytopenia + > 3 areas of lymphoid enlargement
Stage C: Anaemia and/or thrombocytopenia

Treatment

- Stage A no treatment
- Stage B or C: **Oral chlorambucil** to ↓ lymphocyte count. &↓ lymph node & spleen size.
- **Fludarabine** may be used either alone or in combination.
- ~~Corticosteroids for bone marrow failure or autoimmune hemolytic anaemia or~~ thrombocytopenia.
- Splenectomy may improve low blood counts due hypersplenism.
- Supportive treatment: as above

Complications

- Hypogammaglobulinemia leading to bacterial and viral recurrent infections
- Warm autoimmune hemolytic anemia in 10-15% of patients
- Transformation to high-grade lymphoma (**Richter's transformation**)

Prognosis

- 50% of pts die of infection and 30% of causes unrelated to CLL.
- The median survival is 5-6 years.
- CLL rarely progresses to acute leukemia.

Hairy cell leukemia: is rare (male/female ratio of 4 : 1. peak age of 55 years), presents with splenomegaly and pancytopenia. "Hairy cells' are present in bone marrow and blood. Infections are frequent. They are B cells which stain for tartrate resistant acid phosphatase (TRAP). Effective treatments include 2-chloro-deoxyadenosine (2-CDA) deoxycoformycin. interferon-α and splenectomy.

Lymphoma

Definition: Lymphoma is a neoplastic proliferation of lymphoid cells originating in lymph nodes or other lymphoid tissue (spleen or mucosa-associated lymphatic tissue): thymus

there D overlap ε leukemia

Epidemiology

Hodgkin lymphoma

- Bimodal distribution with major peak between 20-30 yrs & minor peak at 60 yrs.
- Gender: more in **males**

Non-Hodgkin lymphoma

- Age: more in elderly
- Gender— More in **males**

Etiology

- The cause is not known. & Both have familial aggregation.

➢ **Hodgkin lymphoma:**

- EBV
- Wood workers

➢ **Non-Hodgkin lymphoma**

- EBV & Malaria in Burkitt's lymphoma. MALTOMA
- *Helicobacter pylori* infection in gastric lymphoma.
- Environmental factors as **radiation** & drugs (e.g. phenytoin).
- Autoimmune disease:
  - Sjögren's syndrome
  - Autoimmune thyroiditis hashimotothyroditis
  - Celiac disease
- Immune suppression (e.g. AIDS → CNS lymphoma, post-transplant).
- Alkalytic agent

Histological classification

➢ **Hodgkin lymphoma**

- **Reed-Sternberg (RS)** cells are characteristic and are of B-cell origin.
- Histological subtypes **(Rye classification):**
  1. *Nodular sclerosing HL: most common,* young ♀, mediastinal disease.
  2. *Mixed cellularity HL:* older pts, extensive disease.
  3. *Lymphocyte rich classical HL:* uncommon; limited disease.
  4. *Lymphocyte depleted HL:* rare; poor prognosis.

➢ **Non-Hodgkin lymphoma**

- NHL >80% are B cells. & <20 % are T cell or unclassified.
- There are two histological categories: low mortality but resistance to Rx
  1. Low-grade NHL: this is indolent; but may become aggressive with time; it resists treatment survival may be prolonged (median survival is 10 yrs).
  2. High-grade NHL: this form carries higher early mortality but paradoxically is more responsive to treatment. high mortality but response to Rx

Clinical Picture

Differences		
Clinical feature	**Hodgkin's disease**	**Non-Hodgkin**
Prevalence	Less common	More common
Age	Bimodal (25, 60)	65-70 (older mean age)
Common location	Cervical and supraclavicular nodes	Abdominal, mediastinal, and supraclavicular
Spread	Contiguous	Non-contiguous
Extranodal disease	Uncommon	Common
Systemic symptoms	Common	Uncommon
SVC syndrome	Rare	Common
Airway obstruction	Rare	Common

Hodgkin

- Enlarged, **Painless** rubbery **lymphadenopathy** (typically cervical & supraclavicular) is characteristic presentation. They may fluctuate in size. Alcohol ingestion may precipitate pain.
- **Generalized Pruritis.**
- **Constitutional symptoms** (Fever, weight loss, and drenching night sweats) in 30%.
- Hepatic and splenic enlargement may occur.
- **Pel-Ebstein** fever: occurs intermittently and recurs at variable intervals over several days or weeks.

Non-Hodgkin

- Enlarged, painless lymphadenopathy but are Non-contagious and multicentric.
- Extranodal involvement is common. [GIT, Bone, Lung, CNS]
- Bone marrow involvement is more common in low grade than high grade.

Investigations

Hodgkin

- CBC → Anemia (normochromic, normocytic).
  → Leukocytosis or Lymphopenia (Poor prognosis) ± eosinophilia.
- ↑ ESR , ↑ Uric acid.
- ↑ **LDH** (useful as prognostic marker and for monitoring response)
- Radiology: CT to look for other LN groups [Mediastinum, Abdomen, Pelvis]
- Bone marrow aspiration **or biopsy**.

Non-Hodgkin

In addition to the changes seen in HL, NHL may cause:

- Pancytopenia as a result of bone marrow involvement → bone marrow failure.
- Paraprotein IgG & IgM may be raised

In both diagnosis is by LYMPH NODE BIOPSY

Staging

Ann Arbor staging system for lymphoma (HL & NHL)	
Stage IA or IB	Single lymphoid area or extranodal site (stage IE)
Stage IIA or IIB	Two lymphoid areas or extranodal sites on the same side of the diaphragm
Stage IIIA or IIIB	Lymphoid areas (including the spleen) on both sides of the diaphragm
Stage IVA or IVB	Diffuse involvement of an extranodal organs (liver, bone marrow)
• A: No symptoms • B: > 10% weight loss, drenching night sweats, or unexplained fevers > 38° C • E: involvement of a single extranodal site contiguous or proximal to known nodal site.	

Treatment & Prognosis

Hodgkin

- Stage IA and IIA treatment is with local radiotherapy
- Higher stages Chemotherapy ± Radiotherapy
- Chemotherapy regimen is:
  ChlVPP **(Chlorambucil, Vinblastine, Procarbazine, Prednisolone)**
- Side effect is infertility. — leukemia + breast cancer

Prognosis

➢ **Cure in >90% of stage I and II,** but only 50% of stage IV pts.

➢ Poor prognostic factors: •Age > 45 •Male •B symptoms •Lymphocyte-depleted histology •Higher stage •Very bulky lymphadenopathy •Hb < 10.5 g% •Leukocytosis •Lymphopenia • ↑LDH

Non-Hodgkin

Paradoxically, aggressive tumors respond more to treatment and are more likely to be cured than indolent tumors.

- *Radiotherapy*→ For localized stage I disease.
- *Chemotherapy:*
  - Low grade: Chlorambucil (better life but not longer).
  - High grade: **CHOP regimen** (Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone).
- *Monoclonal antibody therapy* → anti-CD20 antibody Rituximab. Work synergistically with chemotherapy.
- *Bone marrow Transplantation* → for relapsed pts.

Prognosis

Poor prognostic factors: • Bulky disease • Multiple sites of extranodal involvement • Age • Performance status • ↑LDH level •β2 microglobulin level.

Multiple Myeloma

Definition

Multiple myeloma (MM) is a malignant disorder of plasma cells characterized by:

1. A monoclonal paraprotein in serum and/or urine
2. Bone changes leading to pain and pathological features
3. Excess plasma cells in the bone marrow.

Epidemiology

- **Age**: median age at diagnosis 71 years
- **Gender**: more in males
- Race: more in black

Etiology and pathogenesis

- The etiology is **unknown.** The cell of origin is B-lymphoid cell.

Clinical features

- Features resulting from plasma cell proliferation:
  1. Skeletal involvement: **Bone pain**, especially lower backache is the most common feature. Pathological fracture may occur.
  2. **Hypercalcemia** is a common complication results from bone destruction, it presents with thirst, polyuria, constipation.
  3. Marrow infiltration→features of bone marrow failure.
- Features resulting from the paraproteins:
  1. Infection: due to lack of normal immunoglobulins.
  2. **Amyloidosis** may cause macroglossia, hepatosplenomegaly, cardiac or renal.
  3. Hyperviscosity (rare)
- **Renal failure:** occurs in 30% of pts and is caused by hypercalcaemia, infection, deposition of paraprotein or light chains, uric acid or amyloidosis.

Investigations

- **CBC**: Anaemia ± neutropenia ± thrombocytopenia.
- **ESR** is often >100 mm/h.
- **Blood film** Leukoerythroblastic picture may be present.
- **Bone marrow** shows > **10% plasma cells**.
- Laboratory:
  - ↑ **Serum paraprotein [IgG** in 70% or **IgA].**
  - **Bence Jones protein** (light chains) in urine .
  - Serum β_2-microglobulin ↑ (Poor prognosis)
  - Serum alkaline phosphatase usually normal.
  - ↑ serum Calcium
- **Radiology**:
  - **X-rays: Punched out lesions**
  - **CT scan or MRI** shows lytic lesions typically in skull and axial skeleton.

Treatment

- Asymptomatic pt no Rx. But if symptomatic:
- *Chemotherapy:* [**Thalidomide** OR Melphalan] + Prednisolone
- *Radiotherapy*: for bone pain.
- Autologous stem cell transplants improve quality of life and prolong survival

Supportive care:

- Allopurinol & Hydration to prevent hyperuricemia which may cause renal failure.
- Hydration, steroids and bisphosphonates for hypercalcaemia.
- Plasmapheresis for hyperviscosity.

Prognosis

- Most patients relapse and median survival is 40 months from diagnosis.
- Poor Prognostic factors: ↓ Hb, ↑ serum β_2M, ↑ serum creatinine, ↓ albumin.

~~Waldenstrom's macroglobulinaemia~~

Uncommon disease seen in older men. It is a plasma cell malignancy characterised by the secretion of a monoclonal **IgM** paraprotein

Characteristic feature:

- Monoclonal IgM paraproteinemia
- Hyperviscosity syndromes are common e.g. visual disturbance, DVT
- There is Hepatosplenomegaly and Lymphadenopathy

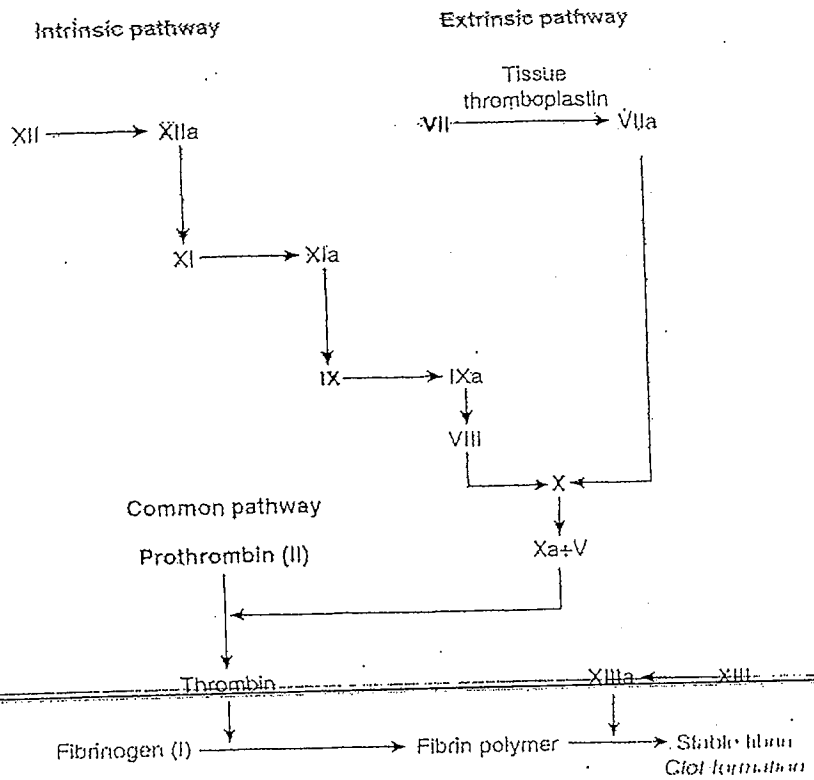
Disorders of Hemostasis

Hemostasis requires normal function of:

1. Blood vessels.
2. Platelets.
3. Clotting factors.

Differentiating between Platelet disorders and Clotting disorders		
	Platelet disorders	Clotting disorders
History	**Immediate mucocutaneous bleeding:** 1. Epistaxis 2. Gingival 3. Gastrointestinal bleeding 4. Menorrhagia	**Delayed deep-tissue bleeding and hemarthrosis**
Examination	Petechiae and purpura	Hematomas and hemarthrosis
Lab	Bleeding Time	PT, aPTT

Laboratory and Clinical Findings in Coagulation Disorders						
Disorder	aPTT	PT	Bleeding time	Platelet Count	Petechiae	Hemarthroses
Factor VII, IX deficiency	Prolonged	Normal	Normal	Normal	No	Yes
von Willebrand's	Prolonged	Normal	Prolonged	Normal	No	Rare
Thrombocytopenia	Normal	Normal	Prolonged	Low	Yes	No
Platelet function defect	Normal	Normal	Prolonged	Normal	Yes	No
Vitamin K deficiency	Prolonged	Prolonged	Normal	Normal	Yes	Yes
DIC	Prolonged	Prolonged	Prolonged	Low	Yes	Sometimes



Prothrombin time: it is done by the addition of a substitute equivalent to tissue factor (tissue thromboplastin) which stimulate factor VII i.e. *Extrinsic pathway*.

INR (International normalized ratio): Because of differences between different batches and manufacturers of tissue factor (it is a biologically obtained product); the INR is adevised to standardize the results.
Each manufacturer gives an ISI (International Sensitivity Index) for any tissue factor they make. The ISI value indicates how the particular batch of tissue factor compares to an internationally standardized sample.

Partial thromboplastin time: Partial thromboplastin is a phospholipid emulsion equivalent to platelet phospholipid which stimulate factor XII i.e. *Intrinsic pathway*.

Hemophilia

Types

Hemophilia A is due to a deficiency of factor VIII.
Hemophilia B (Christmas disease) due to a deficiency of factor IX.

Epidemiology

- Hemophilia A & B are X-linked recessive disorder.
- Hemophilia A & B have similar clinical picture, but hemophilia B is four times less common and usually milder than hemophilia A
- Up to 30% of patients have no family history of the condition.

Clinical features

- Spontaneous bleeding, especially into joints (hemarthroses) and muscles.
- Onset in early childhood (e.g. postcircumcision).
- Increased risk of postoperative or post-traumatic hemorrhage.
- Chronic debilitating joint disease caused by repeated bleeds.

Investigations

- Prolonged APTT
- Bleeding time, prothrombin time, and von Willbrand factor level are normal.
- Plasma factor VIII reduced (< 1 % in severe cases, but up to 10% in mild cases).
- Carriers have 50% of normal VIII. DNA analysis can detect carriers.

Treatment

- Infusions of factor VIII concentrate to elevate the pt's level to 20-50% of normal for severe bleeding.
- Level is raised to and maintained at 80-100% for elective surgery.
- Desmopressin [Vasopressin analogue]: it ↑ endogenous factor VIII, use in mild case
- Avoid aspirin, other antiplatelet drugs and intramuscular injections.
- Patients should carry a card with details of their condition.

Complications of treatment

- HIV and hepatitis B & C.
- Neutralizing antibodies to factor VIII in 15% of severe patients may require immunosuppressive therapy, treatment with porcine factor VIII, or plasma exchange.

Factor IX deficiency (hemophilia B, Christmas disease)

Clinical picture. Diagnosis & treatment are similar to hemophilia A. Except that factor IX concentrate is used for treatment and desmopressin is not effective.

Acute bleeding → Fresh frozen plasma: contains both factors VIII and IX
→ Cryoprecipitate [made from the precipitate of thawed frozen plasma] :contains factor VIII but does not contain factor IX.

von Willebrand's disease (vWD)

most common coagulation defect

Epidemiology

vWD is the most common inherited bleeding disorder, affecting 1% of population.

Types of vWD:

may autosomal recessive but very rare

- Type 1: Partial deficiency of vWF (autosomal dominant) most common.
- Type 2: Defect in vWF.
- Type 3: Complete deficiency of vWF. (autosomal recessive) most severe.

Pathophysiology and clinical presentation

The vWF is protein synthesized by endothelial cells & megakaryoctyes and it has 2 functions:

- vWF adhesive link between platelets and the injured blood vessel wall →clinical features include immediate, mucocutaneous (i.e., platelet-type) bleeding: skin bruising, epistaxis and menorrhagia.
- vWF functions carrier for factor VIII → clinical features of delayed, deep-tissue, post-trauma (i.e., coagulation-type) bleeding

- aggrigation of plt
- carrier protein for factor 8 → coagulation defect

this why have 2 clinical picture

Diagnosis

- ↓ von Willbrand factor.

Investigations

- **bleeding time:** prolonged due to decreased platelet function
- **aPTT**: prolonged due to decreased factor VIII.
- Other tests of platelet aggregation are normal.

PT normal

Treatment

- Desmopressin which raises vWF in mild disease.
- Factor VIII/vWF concentrate in severe disease.
- Cryoprecipitate or plasma contain VIII/vWF.

Thrombophilia

It occurs due to deficiency of body anticoagulant protein [Antithrombin III, Protein C, Protein S]

inhibit thrombin

Antithrombin III deficiency

• Autosomal dominant. Function of Antithrombin III inhibition of thrombin, factor X factor IX, XI.

Clinical Features

- Recurrent venous thromboses is common. Arterial thromboses are uncommon.
- Heparin works by binding to antithrombin III, enhancing its anticoagulant effect by inhibiting the formation of thrombin and other clotting factors. Patients with antithrombin III deficiency may therefore by resistant to heparin treatment

Management: Lifelong warfarinisation +heparinisation during pregnancy.

- antithrombin III concentrates (often using during surgery or childbirth)

reccurent thrombo emboliom

occure after viral infection

Idiopathic thrombocytopenic purpura ↓ plt

Autoimmune disease

Definition: ITP is an immune mediated reduction in the platelet count. Antibodies are directed against the glycoprotein IIb-IIIa or Ib complex. In children it is usually acute and self-limited but in adults is chronic and less likely to resolve without therapy.

Epidemiology

Age—20-40ys
Gender— females (M/F ratio 1:4)

plt unit = 10/000

Clinical manifestation

Excessive bleeding caused by thrombocytopenia may be:

- Mucosal (epistaxis, gingival, gastrointestinal bleeding or menorrhagia)
- Skin (purpura, petcchiae and echymoses).
- Rarely cerebral hemorrhage may occur when the platelet count is <10x10^9/L.

A palpable spleen strongly suggests that ITP is not the etiology for the thrombocytopenia, because < 3% of pts had an enlarged spleen.

may occure in ITP but very rare ↘ SLE hypersplenism

Investigations

- **CBC**: Platelets low, often < 20 x 10^9/L.
- **Bone marrow** is normal or increased numbers of megakaryocytes. (This should be done before starting steroids in order to rule out leukemia)
- **Bleeding time is increased**.
- PT and APTT are normal, fibrinogen is normal.
- Antiplatelet autoantibodies (usually IgG)

if plt < 10 bleeding in #gs

↑ megakaryocyte platelet transfusion

Treatment

- Oral prednisolone (80% of patients respond) after 3m if no response splenectomy
- IV immunoglobulin causes temporary rise in platelet count.
- Splenectomy if platelets < 30 after 3 months of steroid therapy
- Immunosuppressive therapy (e.g. azathioprine, cyclophosphamide, cyclosporine A, rhesus anti-D, and vincristine) may be used.

↑ bleeding ⟶ plt.

DDx of thrombocytopenia:

1. ↓ **Production:** BM damage (drugs, irradiation) BM failure (aplastic anemia), BM invasion (carcinoma, leukemia, amyloidosis and fibrosis).
2. ↑ **Destruction:**
   - Hypersplenism
   - Autoimmune destruction by antibodies: ITP or SLE, Lymphoma, HIV – ANA ↑ hepatitis B-C HB – Syphilis
   - Disseminated intravascular coagulation (DIC): Plt consumption with coagulation factor depletion (prolonged PT, PTT) and fibrinolysis (↑ d-dimer). *Causes*: Infection (meningococcal), Extensive burns, Trauma, Metastatic carcinoma, [AML M3]).
   - *Thrombotic thrombocytopenic purpura* (TTP)—rare disorder characterized by microangiopathic hemolytic anemia, fever, thrombocytopenia, renal dysfunction (and/or hematuria), and neurologic dysfunction caused by failure to cleave vWF.

affect the brain (encephalopathy) mainly adult

when take biopsy or surgery must Pt → 60

only affect kidney — hemolytic uremic syndrom in pediatric ← history of diarrhea DuroDra – Hgb ↓ – urea ↑

Anticoagulant therapy

Heparin

- Heparin is not absorbed orally so it's given subcutaneously or intravenously.
- Heparin activates antithrombin (AT) which irreversibly inactivates Prothrombin, Xa, IXa and XIa. It also impairs platelet function.

Types:

Unfractionated heparin (UFH)	Low molecular-weight (LMW <5000)
Activates antithrombin→ irreversibly inactivates prothrombin Xa, IXa and XIa.	Greater ability to inactivate Xa and less effect on thrombin.
Short half-life so given by IV infusion	Long half-life so given once daily
More side effects	Same but Less likely

Indications

1. Acute venous thrombosis, e.g. DVT and pulmonary embolism (PE). Continuous intravenous infusion of UFH for 5-7 days until warfarinized. Subcutaneous LMW heparin is equally effective. Warfarin is usually started 1-2 days after heparin.
2. Acute peripheral arterial occlusion.
3. Prophylaxis of thrombosis (DVT) in surgical patients, or pts on renal dialysis
4. Pregnancy. (Warfarin is teratogenic)
5. Maintaining patency of indwelling lines and catheters.

Monitoring

UFH is monitored by APPT which should be maintained at 1.5-2 x normal.
LMW heparin therapy is not normally monitored. [But can be monitored by

Side effects

1. Hemorrhage. Heparin has a short half-life (1 h); levels fall rapidly when infusion stopped. **Protamine sulphate** will reverse heparin immediately, but must be used with caution as it can cause hemorrhage at high dosage.
2. Long-term therapy (>2 months) can lead to osteoporosis.
3. Thrombocytopenia, which is antibody-mediated.

Warfarin. Given orally

Vitamin K promotes the γ- carboxylalion of glutamic acid residues of factor II, VII, IX and X; warfarin inhibits this enzyme. Full anticoagulation occurs 72h after starting therapy. Protein C and S levels also fall and this initially (first 2-3 days) leads to an increased risk of thrombosis and may lead to skin necrosis.

Control and monitoring: By PT and expressed as (INR). Treatment aim to maintain INR at 2.0-3.5 level depending on indication.

Indications

1. Treatment of DVT, pulmonary embolism, systemic embolism (3-6 months).
2. Prophylaxis against thrombosis in patients with atrial fibrillation, prosthetic valves, arterial grafts, and in patients with inherited or acquired predisposition.

Side effects: • Hemorrhage • Skin necrosis

Reversal of action: Patients with hemorrhage and a raised INR should receive fresh frozen plasma. If less severe vitamin K (10 mg i.v.).

Notes on Hematology

Splenomegaly

- Spleen lies under 9th, 10th, & 11th rib with anterior margin reaching anterior axillary line
- Sizes: Spleen is palpable if it's 3 times more enlarged than normal
- Massive Splenomegaly is >8cm below costal margin or crosses midline
- Not every palpable liver is pathological but any palpable spleen is pathological

Massive splenomegaly >8c	Moderate splenomegaly 4-8cm	Slight < 4cm
1- Myelofibrosis 2- CML 3- Malaria 4- Kala-azar 5- Gaucher's disease	Causes of Massive and: 1- Hemolytic anemia 2- Lymphoproliferative dis 3- Portal hypertension 4- Splenic vein thrombosis	Causes of Massive & Moderate + 1- Infections [IMN, SBE] 2- Blood dis [PRV, ITP, Pernicious anemia, SLE, Felty's Sarcoidosis, Amyloidosis]

- *Hypersplenism*:
  - *Definition:* its condition characterized by splenomegaly + cytopenia(s) + hyperplastic bone marrow + a response to splenectomy.
  - It occurs as a result of that components of the blood (RBC, WBC, Plt) are removed at an abnormally high rate by the spleen → low circulating levels.

- Generalized Lymphadenopathy
  - *Definition:* It's a lymphadenopathy that involves 2 or more non-contiguous sites
  - DDx:
    1- Viral→ infectious mononucleosis syndromes (EBV, CMV) and HIV
    2- Bacterial→ TB, Syphilis
    3- Parasitic→ Toxoplasmosis
    4- Immunologic diseases→ RA, SLE and Sarcoidosis
    5- Malignant diseases→ Hodgkin's disease, non-Hodgkin's lymphomas, and leukemias or secondaries for a solid tumor
    6- Drug→ Phenytoin
  - Note :Submandibular nodes <1 cm and inguinal nodes of < 2 cm, are normal

normal size .5 cm

Leukemoid Reaction: Extreme elevation of leukocyte count (>50,000/μL) composed of mature and/or immature neutrophils.
Causes: Infection (tuberculosis), *Hemolysis* (severe), *Malignant neoplasms* (esp. carcinoma of the breast, lung, kidney)).
Leukemoid reaction is distinguished from chronic myeloid leukemia (CML) by measurement of the leukocyte alkaline phosphatase (LAP) level: ↑ in leukemoid reactions, & ↓ in CML.

Poikilocytosis [abnormal RBC shapes]	
Pencil cell	Iron deficiency anemia Thalassemia
Target cell [central & outer rim of staining with intervening ring of pallor]	Thalassemia Liver disease Fe deficiency Hyposplenism
Elliptocytes [elliptical]	Hereditary Elliptocytosis
Sickled cells [elongated, crescentic]	Sickle cell anemias
Spherocytes [small hyperchromic cells]	Hereditary Spherocytosis
Bite cells	G6PD deficiency
Schistocytes [fragmented cells]	Mechanical hemolysis
Teardrop cells	Myelofibrosis Myelophthisis
Echinocytes (burr cells) [Regularly spiculated]	Uremia
Acanthocytes (spur cells)[Irregularly spiculated]	Abetalipoproteinemia Sever liver disease
Leukoerythroblastic Reaction [immature leukocyte + nucleated RBCs]	Myelophthisis: invasion of the bone marrow by tumor. Myelofibrosis Hemorrhage or hemolysis

RBC Inclusions	
Howell-Jolly bodies [basophilic cytoplasmic inclusion & represents a residual nuclear fragment]	Asplenic patient Megaloblastic anemia
Heinz bodies [inclusions of precipitated hemoglobin]	Asplenic patient Thalassemia G6PD deficiency
Basophilic stippling	Lead poisoning
WBC Inclusions	
Hypersegmentation [neutrophil nuclei contain more than the usual 2–4 lobes]	Megaloblastic anemia
Auer rods [eosinophilic, rodlike cytoplasmic inclusions]	Acute myeloid leukemia
Toxic granulations & Döhle bodies	Bacterial infection

➢ **Indications for bone marrow aspiration:**

1. To confirm the diagnosis of iron deficiency anemia or megaloblastic anemia if the diagnosis is in doubt or the patient does not respond to treatment.
2. To investigate unexplained anemia, leukopenia, or thrombocytopenia.
3. To investigate suspected leukemia, or myeloma or other hematological malignancies.
4. To monitor response to treatment of leukemia
5. Work up of some cases of fever of unknown origin

➢ **Indications for bone marrow biopsy:**

1. Dry tap on aspiration (A dry tap is pathological and of diagnostic value)
2. Performed in addition to aspiration for pancytopenia (aplastic anemia)
3. Lymphomas, or Metastatic tumor
4. Granulomatous infection (e.g., mycobacteria, brucellosis, histoplasmosis)
5. Myelofibrosis
6. Lipid storage disease (e.g., Gaucher's, Niemann-Pick)

Leukocytosis > 11,000					
	Neutrophilia > 10,000/mL	Lymphocytosis >5000/mL	Monocytosis >800/mL	Eosinophilia >500/mL	Basophilia >100/mL
Infection	Bacterial	Viral and some bacteria: TB, Syphilis, Brucella, Pertussis		Parasitic	
Malignancy	Myeloproliferative	Lymphoproliferative	Myeloproliferative		
Other	**Corticosteroid** MI Exercise	Adrenal crisis Autoimmune [RA]	Crohn's disease	Allergy **Churg-Strauss**	Allergy

Leukopenia <4000				
	Neutropenia <2000/mL	**Lymphopenia** <1000/mL	**Monocytopenia** <100/mL	**Eosinopenia** <50/mL
Infection	Viral **Typhoid** Brucella Miliary TB	Viral		
Drug	**Anti-thyroid** **Thiazide** **Immunosuppressive**	**Corticosteroid** **Immunosuppressive**		
Malignancy	Bone marrow failure: aplastic anemia, Acute leukemia, Myelophthisis Myelofibrosis			

pancytopenia + vit. B12 def.